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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,186	07/30/2001	C. Frank Bennett	ISPH-0585	6392

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LICATLA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER
MCGARRY, SEAN

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/21/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,186	BENNETT ET AL.	
	Examiner	Art Unit	
	Sean R McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-10,14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 7-10, 14, 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1 and 6-15 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-23 of U.S. Patent No. 6,335,194. This rejection has been withdrawn in view of the Terminal disclaimer filed 12/24/02.

Claims 7 and 8 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,165,788. This rejection has been withdrawn in view of the Terminal Disclaimer filed 12/24/02.

Claim 6 was rejected under 35 U.S.C. 103(a) as being unpatentable over over Altieri et al. [WO 98/22589] in view of Baracchini et al [US 5,801,154]. This rejection has been rendered moot in view of the cancellation of claim 6.

Claims 1, 7-10, 14, and 15 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro methods, does not reasonably provide enablement for in vivo/therapeutic applications. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant invention is drawn to the treatment and in vivo application of antisense oligonucleotides for modulation of various biological systems (cell cycle, cell

proliferation, apoptosis, cytokinesis, for example) via the inhibition of Survivin in a whole animal.

The instant specification, as filed provides guidance for the inhibition of Survivin in cell in culture. In Example 25 skin grafts in immunodeficient mice treated with SEQ ID NO: 250 indicates that there was a reduction of Survivin protein as per an immunostimulatory assay. The Example does not show the level of Survivin reduction or if the reduction was statistically significant, for example. It is not clear from this example how such an observation correlates to the treatment of various disease states with Survivin targeted antisense.

The art of nucleic acid based therapy is an unpredictable art. Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can

be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*."

Jen et al [STEM CELLS Vol. 18:307-319, 2000] Discuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that

progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

The instant specification does not provide one in the art with guidance such that the obstacle exemplified above have been overcome such that one in the art could predictably treat the broad range of diseases instantly contemplated. The quantity of experimentation would include determining treatment regimes de nov and further to overcome the general problems of nucleic acid therapy de novo as they apply to the specific regimens, for example.

Applicant's arguments filed 12/24/02 have been fully considered but they are not persuasive. Applicant argues that in Example 25 it is asserted that there is no difference observed between treated and control groups and that this indicates that there was significant reduction of the expression of Survivin, and that if that had not occurred then the inventors would have reported that controls and treated [grafts] were not the same.

This line of argument is not clear to the examiner since it appears from the Example that the only difference between the two groups [grafts] was the use of control oligonucleotides in one and Survivin targeted oligonucleotides in the other. It appears that both groups were subjected It is therefor unclear to the examiner how one would expect that the control and test tissues would be expected to be the same. Further, it is unclear, how, in view of the art cited in the rejection of record and the unpredictability of the art as exemplified in the art cited above, how one in the art would correlate the inhibition of Survivin (to what extent the inhibition is, is unclear) via a specific oligonucleotide (SEQ ID NO: 250) in an immunological example to a method of treating cancer (any kind of cancer) with any antisense targeted to Survivin, for example. Applicant asserts that the citations relied upon for evidence of unpredictability in that art do not rise above the evidence presented in the instant Example 25, for example. The scope of the claimed invention is drawn broadly to the modulation (i.e. increase and decrease in expression of Survivin) where the specification only shows a decrease in expression and also is drawn to any route of administration of oligonucleotides, where the instant specification shows a topical administration to a skin graft and direct administration to cells in culture. It is unclear, in view of the art cited in the rejection, how the disclosure of these narrow embodiments correlates to the broad scope instantly claimed, for example, since the art teahes that delivery of oligonucleoyides in a treatment is a significant obtacle in the art. The scope of the instant claims still embrace methods of treatment.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (703)305-7028. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Sean McGarry
March 10, 2003